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10/810,358	03/26/2004	Ker-Sang Chen	9188R&	1244

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THE PROCTER & GAMBLE COMPANY
Global Legal Department - IP
Sycamore Building - 4th Floor
299 East Sixth Street
CINCINNATI, OH 45202

EXAMINER	
SHAFER, SHULAMITH H	
ART UNIT	**PAPER NUMBER**
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/810,358	CHEN ET AL.	
	Examiner	Art Unit	
	SHULAMITH H. SHAFER	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *1* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-8 and 11-45* is/are pending in the application.

4a) Of the above claim(s) *13-15 and 24-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5-8,11,12,16-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims:

The amendment received 12 September 2008 has been entered. Claims 2, 4, 9 and 10 are canceled. Claims 1, 3, 5-8, 11-45 are pending in the instant application. Claims 1, 3, 11-13, 22, 28-31, 35, 37-44 have been amended and the amendment made of record. Claims 13-15 and 24-45 are withdrawn as being drawn to a non-elected invention.

Claims 1, 3, 5-8, 11, 12, and 16-23 are under consideration.

In response to Election of Species requirement, of 15 June 2006, applicants elected a probiotic as the compound inducing in vitro stimulation. Upon further consideration, this requirement for species election is withdrawn.

Claim Interpretation

Upon further consideration, the Examiner has interpreted claim 22 as **not** written so as to invoke 112, 6th paragraph. The MPEP (§ 2181) states:

> A claim limitation will be presumed to invoke 35 U.S.C. 112, sixth paragraph, if it meets the following 3-prong analysis:
>
> (A) the claim limitations must use the phrase "means for" or "step for;"
>
> (B) the "means for" or "step for" must be modified by functional language; and
>
> (C) the phrase "means for" or "step for" must not be modified by sufficient structure, material, or acts for achieving the specified function.

As the claim does not specifically recite the phrase “means for” or “step for”, it does not meet the 3-prong analysis set forth in the MPEP. It will therefore not be considered to invoke 35 U.S.C. 112, 6th paragraph. The Examiner regrets any confusion as a result of the inadvertent error.

Withdrawn Rejections

The rejection of Claims 1, 3, 5-8, 11, 12, and 16-21 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in light of Applicants' amendment to the claims.

The rejection of Claim(s) 1, 3, 5-8, 11, 12 and 16-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement (**scope of enablement rejection**) is withdrawn, in part, in light of Applicants' amendment to the claims to recite specific anti-inflammatory and pro-inflammatory cytokines and to recite biological sample "from the bowel, ….peripheral blood mononuclear cells with *in vitro* stimulation, gut lymphoid tissues without *in vitro* stimulation, gut lymphoid tissues with *in vitro* stimulation and combinations thereof;"

Maintained/New Grounds for Rejections

35 U.S.C. § 112, Second Paragraph:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 5 is dependent upon a rejected claim; thus the metes and bounds of the claim cannot be determined.

Claim 22 remains rejected under 35 U.S.C. 112, 2nd paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicants traverse the rejection (Response of 12 September 2008, paragraph page 12 bridging page 13, 4th paragraph). The reasons for the traversal are:

1. Claim 22 does specify two elements: a kit comprising a first measuring element or system for measuring the level of at least one anti-inflammatory cytokine in a biological subject before treatment and at least one time point after or during treatment and a second measuring element or system for measuring the level of at least one pro-inflammatory cytokine in a biological sample from said subject before treatment and at at least one time point after or during treatment.

2. Since the claim will be evaluated under 112, 6th paragraph an element in a claim for a combination may be expressed as a means or step for performing a specified function without the recital of structure, material, or acts in support thereof, and such claim shall be construed to cover the corresponding structure, material, or acts described in the specification

3. Claim 22 does specify the interrelationship between the two measuring elements. Both measuring elements or systems measure cytokines. They are related in that both are needed in order to measure the level of a type of cytokine and the two levels are then compared.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

With respect to 1 and 3: The elements or systems recited in the claim do not comprise any structural limitations or concrete elements as would be commonly considered to be components of a kit, which is understood to be a product (see In re Venezia 530 F.2d 956 CCPA 1975); rather the claim recites unspecified systems or elements for performing steps to be used in the method of the claimed invention *i.e.*, the claim is directed to an unspecified method of measuring pro and anti inflammatory cytokines, and does not recite components or elements of a kit to be utilized in measuring said cytokines.

Additionally, the interrelationship between the two systems comprises a computational step, determination of a ratio, and not a recitation of how the two components are related.

With respect to 2: As stated above, Claim 22 is no longer evaluated under 112, 6th paragraph (See discussion above.)

Claim 23 is included in this part of the rejection as dependent upon a rejected claim.

35 U.S.C. § 112, First Paragraph:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of Claim(s) 1, 3, 5-8, 11, 12 and 16-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement (**scope of enablement rejection**) is maintained for reasons of record and for reasons set forth below.

The specification, while being enabling for a method of determining the efficacy of a treatment of inflammatory diseases of the bowel in mammals *in vivo*:

a. wherein the cytokine levels are measured before and after treatment in a biological sample wherein the biological sample comprises a biopsy sample from the bowel, peripheral blood mononuclear cells that have been stimulated in vitro, gut lymphoid tissues with *in vitro* stimulation or gut lymphoid tissues without *in vitro* stimulation and

b. wherein a treatment comprises administration of a treatment and/or a composition other than direct administration of anti-inflammatory cytokines or compositions which directly inhibit cytokines

does not reasonably provide enablement for a method of determining the efficacy of a treatment of inflammatory diseases of the bowel in mammals *in vivo*:

c. wherein cytokine levels are measured in a biological sample wherein the biological sample comprises, peripheral blood mononuclear cells that have **not** been stimulated and

d. wherein a treatment comprises direct administration of anti-inflammatory cytokines or compositions which directly inhibit pro-inflammatory cytokines

Applicants traverse the rejection (Response of 12 September 2008, paragraph page 15, 2nd paragraph bridging page 16). The reasons for the traversal are:

1. Applicants assert that the claims as amended are enabled for all of the claimed biological samples and methods as biological samples are recited in the claim.

2. With respect to lack of enablement for measuring response to treatment that involves administering anti-inflammatory cytokines or compositions which interact directly with pro-inflammatory cytokines, applicants assert;

"Even though such treatments may be known, and the subject's response might be due to the administration of an anti-inflammatory cytokine or antibody to a pro-inflammatory cytokine the methods of the Application can still be used to study the subject's response to the treatment, and to determine the effect of the treatment"

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

With respect to 1: The specification teaches a number of biological samples that may be used in the method of the instant invention. Among the biological samples listed are peripheral blood mononuclear cells (PBMC) with or without in vitro stimulation. The disclosure teaches methods of harvesting and collecting such samples [paragraph 0059]. However, the question is not whether one can obtain samples of such cells, but whether the results obtained by measuring changes of pro- and anti-inflammatory cytokines in the cell supernatants in samples (absent *in vitro* stimulation) would be indicative of efficacy of treatment of inflammatory diseases of the bowel. The working

examples in the specification teach only measurement of ratios of anti-inflammatory to pro-inflammatory cytokines in IBS patients' PBMCs upon pro-biotic *in vitro* stimulation [paragraph 0083, 0084]. There are no teachings of measurement of ratios of anti-inflammatory to pro-inflammatory cytokines in IBS patients' PBMC **without** pro-biotic *in vitro* stimulation.

The teachings in the art do not compensate for the lack of guidance in the specification. As stated in previous Office Action, Whiteside (2003. Chapter 61 in The Cytokine Handbook, Vol II, 4th edition, pages 1384-1386 enclosed in previous Office Action) teach that assaying of spontaneous (non-stimulated) production of cytokines by PBMCs will tend to give false-positive results. Additionally, Bing et al. (1998. World J Gastroenterology 4:252-255) teach that spontaneous TNFα (one of pro-inflammatory cytokines recited in the claims) and spontaneous sIL-2r (identified by Bing et al as an index of IBD activity (page 252, 2nd column, 3rd paragraph)) production were not significantly different between ulcerative colitis and control groups. Thus one of skill in the art, aware of the teachings in the art, would not predict that measurement of changes of ratios of anti-inflammatory to pro-inflammatory cytokines in IBS patients' PBMC **without** pro-biotic *in vitro* stimulation would be indicative of changes in patients' disease or conditions or efficacy of treatment.

With respect to 2: Administration of IL-10 or antibodies to pro-inflammatory cytokines are art-recognized methods of treating IBD. These treatments, by themselves, would result in increasing IL-10 levels and/or decreasing pro-inflammatory cytokine levels in biological samples drawn from the patient. These treatments would result in a change in the ratios of levels IL-10 to levels of IL-12 or levels of TNF-α or levels of IFN-γ, but one could not determine if these changes would be indicative of efficacy of treatment or are a result of administration of therapeutic compounds. There are no teachings in the disclosure to enable the skilled practitioner to differentiate between these possibilities without undue experimentation.

35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of Claim 22 under 35 U.S.C. 102(b) as being anticipated by Vignali (2000 Journal of Immunological Methods 243:243-255) is maintained for reasons of record and for reasons set forth below.

Claim 22, given its broadest reasonable interpretation, is drawn to a kit for measuring cytokines in a biological sample from a mammalian subject. There are no structural limitations recited as to the contents of said kit. The claim is not directed to a method, so the intended use of the kit, and a recitation of when such measurements are to be performed is not given patentable weight. The claim does not explicitly recite any specific structural elements or components; thus art which teaches components to be used for measurement of the recited cytokines will anticipate the limitations of the claim.

As previously stated, Vignali teaches a FlowMetrix System of quantifying the concentration of 15 cytokines simultaneously in a 100 µl sample (page 248, 2nd column, section 60). Among the cytokines which may be measured in culture supernatants of stimulated peripheral blood mononuclear cells are IL-4, IFN-γ and IL-12, which are among the cytokines recited in the claims of the instant invention. Once the concentration of cytokines are determined, the ratios may easily be determined by dividing the concentrations of anti-inflammatory cytokines by the concentrations of pro-inflammatory cytokines. The skilled artisan may then draw conclusions by comparing ratios.

Therefore, the teachings of Vignali anticipate all the limitations of claim 22.

Applicants traverse the rejection (Response of 12 September 2008, page 17, 2nd paragraph 3 bridging page 18, 1st paragraph).

The reasons for the traversal are:

Vignali discloses that multiple cytokine levels can be measured simultaneously, but does not disclose a kit for measuring the particular cytokines recited in Claim 22 in a supernatant of cells cultured from a biological sample.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

Vignali teaches use of a FlowMetrix System. This system is sold by Invitrogen as Protein Multiplex Immunoassays. The company states "Biosource now offers over 100 kits for uses with the Luminex xMAP system" (see, for teaching purposes only, http://www.invitrogen.com/content.cfm?pageid+11317&CID=KNC-GOOGLE&s_kwcid=…, downloaded 20 May 2007, enclosed with previous office action). Furthermore, there are no structural limitations recited in the claims as to the contents of said kit. A reasonable interpretation of the claims could interpret a kit to comprise, for example, antibodies to cytokines in a vial or test tube. This system can be used at any time point of a treatment protocol to measure pro- and anti-inflammatory cytokines.

The rejection is therefore maintained.

35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of Claim 23 under 35 U.S.C. 103(a) as being unpatentable over Vignali (2000 Journal of Immunological Methods 243:243-255) as applied to claim 22 is maintained for reasons of record and reasons set forth below.

Applicants traverse the rejection (Response of 12 September 2008, page 18, 4th paragraph 3 bridging page 19, 1st paragraph).

The reasons for the traversal are:

1. Vignali does not disclose a kit, but discloses assay methods and devices and compares them.

2. There is no motivation to create a kit; therefore there is no motivation or expectation of success for creating a kit containing a means for collecting biological samples.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

The claims do not recite any specific component or element for obtaining biological samples. Thus, any instrument such as a pipette or a syringe would meet the limitations of a "means for obtaining said biological samples…."

As discussed above, the system used by Vignali is sold as a kit to measure cytokine levels. Vignali et al teaches use of the FlowMetrix™ assay (kit) to measure cytokine levels in an animal model for toxic shock syndrome. One of ordinary skill in the art would understand that the biological sample must be obtained from the mammalian subject. Therefore, one of ordinary skill in the art would be motivated to include an instrument or sampling device to obtain said biological sample to increase efficiency of utilization of assay to determine cytokine levels.

The rejection is therefore maintained.

The rejection of Claims 1, 3, 5, 16, 17, 19, and 20 under 35 U.S.C. 103(a) as being unpatentable over Togawa et al. (2002 Am J. Physiol, Gastrointestinal

Liver Physiol 283:G187-G195) is maintained for reasons of record and for reasons set forth below.

Applicants traverse the rejection (Response of 12 September 2008, page 20, 2nd paragraph-4th paragraph). The reasons for the traversal are:

1. Togawa details experiments in rats using induced colitis.

2. Togawa does not provide any suggestion or motivation to study before and after results

3. Togawa does not suggest studying ratios of cytokines to establish and analyze shifts in patterns of cytokine levels to evaluate efficacy of treatment.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

The Togawa et al reference teaches the following fact pattern:

1. An experimental rat model of IBD is established by treating rats with TNBS, thus inducing colitis, an inflammatory bowel disease.

2. One group of rats is treated with a test treatment compound (lactoferrin) and a second group, the control group, is treated only with saline.

One of ordinary skill in the art would consider the control group in an animal model to be the equivalent of a human patient before treatment, as recited in the claims.

3. Pro-inflammatory and anti-infammatory cytokines are measured in samples of inflamed colons (biopsy samples) from animals treated with lactoferrin (treatment) or saline (control). The reference teaches measurement of the pro-inflammatory cytokines TNF-α, and IL-1β, and the anti-inflammatory cytokines IL-4, and IL-10 by ELISA assays and comparing cytokine levels in treated rats to cytokine levels in untreated rats. Thus, Togawa et al. teaches changes in levels of pro- and anti-inflammatory cytokines as a result of treatment of IBS; these changes may be indicative of efficacy of treatment for IBS. One of ordinary skill in the art would consider this measurement of efficacy of treatment to be the equivalent of measuring changes in cytokine levels in human patients before and after treatment.

While Togawa et al do not teach measuring the level of anti-inflammatory and pro-inflammatory cytokines before administering treatment, or determining the ratio of levels of anti-inflammatory cytokine to level of pro-inflammatory cytokine before and after treatment, it would have been obvious to the person of ordinary skill in the art at the time the invention was made, treating IBS patients, to measure cytokine levels in a biological sample before administration of treatment and after treatment to assess efficacy of treatment. A person of ordinary skill in the art would have been motivated to make those modifications because Togawa et al suggest clinical experimentation to determine efficacy of the administration of lactoferrin for treatment of IBS. The skilled artisan, following the teaching of Togawa et al, would be motivated to measure cytokine levels before treatment in a clinical setting, instead of measuring levels in control animals in an experimental animal model, as the artisan would be aware of that such study design is a standard protocol in clinical research, and would realize that it would be less expensive and more efficient to test cytokine levels in patients before and after treatment instead of having a control, untreated group of patients as taught by Togawa et al. and comparing said group to treated patients. Furthermore, knowing the results of measurements of cytokine levels (as shown, for example, in Figure 5), one would be motivated to compute ratios of anti-inflammatory to pro-inflammatory cytokines as an easy way of determining shifts in patterns of cytokine levels. One would reasonably expect success because method of measuring cytokine levels in biological samples is well known in the art, and is taught by Togawa et al.

The rejection of Claims 18 and 21 under 35 U.S.C. 103(a) as being unpatentable over Togawa et al. as applied to claims 1, 17 and 20 in view of Vignali et al. (cited above and in previous Office Action) is maintained for reasons of record and for reasons set forth below.

Applicants traverse the rejection (Response of 12 September 2008, page 21, last paragraph bridging page 22, 1st paragraph). The reasons for the traversal are:

While one could analyze the cytokine levels of Towaga with such a system of Vignali, one would not have arrived at the claimed method of determining the efficacy of a treatment of inflammatory diseases of the bowel in mammals *in vivo.* Towaga and Vignali together do not suggest or provide motivation or expectation of success for a clinical method, using samples from a biological subject, in which particular cytokine levels are determined and ratios analyzed, as claimed.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

Togawa et al suggest clinical experimentation to determine efficacy of the administration of lactoferrin, meaning assessing the efficacy of lactoferrin as a treatment for IBS. Togawa et al also teach changes in the levels of anti- and pro-inflammatory cytokines are correlated with lactoferrin treatment. The clinical researcher would be motivated to measure cytokine levels before treatment in a clinical setting, instead of measuring levels in control animals as taught by Togawa et al, since such is standard practice in clinical research, and is more efficient and cost effective, as stated above. Togawa et al teach measuring levels of at least one anti-inflammatory cytokine and at least one pro-inflammatory cytokine in a biological sample by ELISA using assay kits with the quantitative immunometric sandwich enzyme immunoassay technique. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Togawa et al and substitute the multiplex assay taught by Vignali for the ELISA assay taught by Togawa et al. One would be motivated to make this substitution, and anticipate success since both assays involve immunological methods of measuring cytokine concentrations and Vignali teaches a more efficient method of quantifying the concentration of 15 cytokines simultaneously. As stated above, knowing the

results of measurements of cytokine levels, one would be motivated to compute ratios as a way of quickly and efficiently determining shifts in patterns of cytokine levels.

The rejection of Claims 6-8 under 35 U.S.C. 103(a) as being unpatentable over Togawa et al. as applied to claim 1 in view of Blumberg et al. (1999. Current Opinion in Immunology 11:648-656) is maintained for reasons of record and for reasons set forth below.

Applicants traverse the rejection (Response of 12 September 2008, page 22, last paragraph bridging page 23, 1st paragraph). The reasons for the traversal are:

Towaga does not suggest establishing or analyzing any ratios of cytokines, nor particularly the claimed ratios. Blumberg also does not suggest establishing or analyzing ratios of cytokines, nor importance of doing so. Blumberg simply notes that there is likely an on-going balance between pro- and anti-inflammatory cytokines, and their release and activity in body systems in relation to inflammation. Blumberg is simply a review of known animal models of mucosal inflammation and their *potential* relation to human inflammatory bowel disease. Blumberg summarizes which animal models might be better for studying various types of inflammatory bowel disease such as Ulcerative Colitis and Crohn's Disease.

Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons:

Togawa et al. teaches measurement of anti-inflammatory cytokines IL-4 and IL-10 and measurement of pro-inflammatory cytokines TNF-α, IL-1β and IL-6. Blumberg et al note the importance of a balance of pro-inflammatory cytokines such as IFN-γ, TNF, and IL-12 and anti-inflammatory cytokines such as IL-10 and TGF-β in managing and assessing inflammatory bowel diseases. The reference teaches that IL-12 is a key factor in the pathogenesis of the TNBS-

induced colitis model (the model taught by Togawa et al) and induces overproduction of IFN-γ and TNF. Blumberg et al also teach that mucosal inflammation can be viewed as a failure of production of suppressor cytokines such as TGF-β and IL-10. Thus, Blumberg et al teach the importance of the balance (ratio) between pro-inflammatory cytokines such as IFN-γ, TNF, and IL-12 and anti-inflammatory cytokines such as IL-10 and TGF-β. Both Togawa et al. and Blumberg et al. teach the importance of disturbed balance between proinflammatory and anti-inflammatory cytokines in inflammatory bowel disease. Thus, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Togawa et al and substitute measurement of the pro-inflammatory cytokines taught by Blumberg et al (IFN-γ and IL-12) for the pro-inflammatory cytokine taught by Togawa et al (TNF-α, IL-1β and IL-6) and the anti-inflammatory cytokine taught by Blumberg et al (TGF-β) for the anti-inflammatory cytokine taught by Togawa et al (IL-10). One would be motivated to measure changes in cytokine levels, since Togawa et al teach changes in cytokine levels in response to therapeutic administration of lactoferrin. Once measurement of these cytokines is accomplished, the calculation of ratios would be obvious as a way of monitoring changes in the balance of levels of pro- to anti- inflammatory cytokines.

New Rejection:

Claims 11 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Togawa et al. as applied to claim 1 in view of Bing et al (1998. World J Gastroenterology 4:252-255) (cited above).

The teachings of Togawa et al. are outlined in detail above. Togawa et al does not teach a method of determining the efficacy of a treatment of inflammatory disease of the bowel in mammals wherein said biological sample comprises peripheral blood mononuclear cells (PBMC) with *in vitro* stimulation, wherein said in vitro stimulation comprises stimulation with a mitogen.

Bing et al. teach assaying production of inflammatory cytokines such as TNF-α and IL-6 by PBMCs isolated from patients with IBS stimulated by a mitogen, PHA (phytohemagglutinin).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the teachings of Togawa et al and substitute measurement of the pro-inflammatory cytokines and anti-inflammatory cytokines in mitogen-stimulated PBMCs, the system taught by Bing et al, for measurement of cytokines in colonic tissue from control and lacto-ferrin treated animals (equivalent of “before" and “after” measurements of cytokine levels in human patients). One of ordinary skill in the art would have been motivated to make these modifications because the skilled artisan would recognize that it would be simpler and less invasive to obtain PBMCs from blood samples drawn from patients than to obtain biopsies from colon tissue. Once measurement of these cytokines is accomplished, the calculation of ratios would be obvious as a way of monitoring changes in the balance of levels of pro- to anti- inflammatory cytokines. One would have expected success because methods of measuring cytokine levels in cell culture supernatants is well known in the art, and is taught by Bing et al.

***Conclusions**:*

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHULAMITH H. SHAFER whose telephone number is (571)272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner’s supervisor, Manjunath Rao, Ph.D. can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. H. S./
Examiner, Art Unit 1647

/Manjunath N. Rao, /
Supervisory Patent Examiner, Art Unit 1647